



## **The amplitude-integrated EEG (aEEG) in the early prediction of outcome in the very preterm newborn**

Natalucci, Giancarlo

**Abstract:** Amplitude-integrated electroencephalogram (aEEG) is a readily available and practical tool for the assessment of time-compressed electroencephalogram (EEG) trend at the bedside. Its interpretation and its learnability are considerably easier compared to those of conventional EEG. For those reasons, aEEG is now a daily part of clinical surveillance for continuous brain function monitoring of critically ill patients in some neonatal intensive care units (NICU). Another reason for the growing interest in this tool for electrophysiological measures is explained by the fact that continuous brain function monitoring early after birth may represent the possibility to early assess the neurological integrity of the newborn and thus, to early select patient needing neuroprotective intervention and to predict outcome. This has been largely demonstrated for the asphyxiated full-term, but not in similar extent for the preterm newborn, whose aEEG background pattern differs sensibly from that of the full-term newborn. Early detection of newborns at particular risk for cerebral injury and further neurodevelopmental disability (ND) still represents one of the major challenges of preterm medical care. At bedside, the aEEG assessment focuses theoretically on the amplitude variations of the raw EEG, and practically on the recognition of the dominant background pattern of activity, the presence and maturational aspect of cycling activity and the presence of seizure activity. Pathological changes in the aEEG tracing are characterized by a depression of the background pattern, a lack or an inadequate maturation of the cycling activity, and the occurrence of seizures. Today, clinicians increasingly use aEEG also in preterms, an ever-growing NICU patient population at high risk for cerebral injury and thus ND. Recent studies showed that changes in the aEEG pattern are associated with poor outcome in the preterm newborns. However, it still remains to be elucidated how and under which conditions aEEG tracing evolves during the very early life period in this patient population, especially in unstable health condition. Although the subject of the present work is the aEEG, this thesis firstly discusses recent data on the outcome of preterm infants born in Switzerland, in order to bring this population of patients into the reader's focus and to define the consequences of prematurity. Thanks to a solid collaboration between perinatal and follow up centres and an established follow up program in Switzerland we are now able to better analyse representative data concerning the development of preterm newborns on a national level. Swiss outcome data of 2 years old former extremely preterms show that, although more than a third of infants still suffer from moderate or severe ND, the rate of survival without major neurologic sequelae has increased significantly over the last decade, while the mortality rate decreased. Interestingly, while neonatal mortality is predominantly dependent on gestational age, birth weight and antenatal corticosteroids, the outcome at two years of age in children surviving the neonatal period is best predicted by neonatal morbidities like, among others, major brain lesions. There is concern whether prematurity and ND affect late outcome. We provided data on quality of life of former extremely low birth weight preterms at young adulthood born in Switzerland in the early 1980s, showing overall satisfactory results though some observable differences between preterms and community norms. This thesis delineates and discusses the application, the clinical utility of the aEEG as well as its predictive value in terms of short- and long-term outcome of preterm newborns. First, technical aspects concerning the methodology and the assessment of the aEEG tracing are explained, with special focus on the potential aEEG signal confounders that interfere with a correct tracing evaluation. We added information in particular on the influence of sedatives on the course of the aEEG tracing in

newborns. Second, the prediction of neonatal and further outcome of the preterm newborn is detailed discussed. Early recognition of preterm patients at higher risk for adverse outcome is important in order to better setup neonatal care and post-discharge intervention. Neuroprotective studies in preterm infants are being conducted to improve long-term outcome and robust biomarkers would help to guide such interventional strategies and to help parental counselling. This thesis demonstrates that changes in the aEEG background activity can predict short-term outcome in preterm infants. The maturational aspect of the early aEEG background tracing in preterm infants relates to structural brain maturation at term equivalent age as assessed qualitatively by magnetic resonance imaging. A delay in the maturation of cyclic aEEG activity in the preterm newborn may be a sign of the development of a major brain lesion. A review of the results of other studies on the predictive value of aEEG for outcome at early childhood is finally included. In conclusion the results of this thesis indicate that aEEG is a valuable neurophysiologic diagnostic tool for early continuous bedside monitoring of brain function and that its background activity can predict short-term outcome in preterm infants. The assessment of the tracing evolution and the detection of sensitive markers of brain lesion during aEEG monitoring could prove critical for implication of therapeutic assistance. Several clinical conditions and artefactual features may however, alter the aEEG tracing and interfere with its interpretation and consequently the prognostic evaluation. Training in the aEEG assessment and knowledge of the potential aEEG signal confounders is therefore needed in order to better further implement this promising neuromonitoring tool in the NICU.

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**The amplitude-integrated EEG (aEEG)  
in the early prediction  
of outcome in very preterm infants**

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## **1. Summary**

Amplitude-integrated electroencephalogram (aEEG) is a readily available and practical tool for the assessment of time-compressed electroencephalogram (EEG) trend at the bedside. Its interpretation and learnability are considerably easier compared to those of conventional EEG. For those reasons, aEEG is now used routinely to continuously monitor brain function in critically ill infants in some neonatal intensive care units (NICU). Another reason for the growing interest in this electrophysiological measuring tool is that continuous brain function monitoring shortly after birth may represent the possibility to early assess the neurological integrity of the newborn infant and thus, to select patients benefitting from neuroprotective intervention and ultimately to predict outcome. This has been extensively demonstrated for full-term infants with neonatal encephalopathy following perinatal asphyxia, but not to a similar extent for preterm infants, whose aEEG background pattern differs sensibly from that of the full-term infant. Early detection of newborn infants at particular risk for cerebral injury and further neurodevelopmental disability (ND) still represents one of the major challenges of preterm medical care. At bedside, aEEG assessment focuses theoretically on the amplitude variations of the underlying raw EEG, and practically on the recognition of the dominant background pattern of activity, the presence and maturational aspect of cycling activity, and the presence of seizure activity. Pathological changes in the aEEG tracing are characterized by a depression of the background pattern, a lack or an inadequate maturation of the cycling activity, and the occurrence of seizures. Today, clinicians increasingly use aEEG also in preterm infants, an ever-growing NICU patient population at high risk for cerebral injury and thus ND. Recent studies have shown that changes in the aEEG pattern may be associated with poor outcome in the preterm infants. However, it still remains to be elucidated how and under which conditions aEEG tracing evolves during the very early life period in this patient population, especially in unstable health condition.

In the first section, this thesis discusses recent data on the outcome of preterm infants born in Switzerland, in order to bring this population of patients into the reader's focus and to define the consequences of prematurity. Thanks to a strong collaboration between perinatal and follow up centres and an established follow up program in Switzerland, we are now able to better analyse representative data concerning the development of preterm infants on a national level. Swiss outcome

data of 2 years old former extremely preterm infants show that, although more than a third of infants still suffer from moderate or severe ND, the rate of survival without major neurologic sequelae has significantly increased over the last decade, while the mortality rate has decreased. Interestingly, while neonatal mortality is predominantly dependent on gestational age, birth weight and antenatal corticosteroids, the outcome at two years of age in children surviving the neonatal period is best predicted by neonatal morbidities such as major brain lesions, bronchopulmonary dysplasia, and retinopathy of prematurity. There is concern whether prematurity and ND may affect later outcome in adulthood. We provided data on quality of life of former extremely low birth weight preterm infants, born in Switzerland in the early 1980s, at young adulthood, showing overall satisfactory results despite some observable differences between preterms and community norms.

The focus of the second and main section of this thesis is the application of aEEG in preterm born infants. This thesis outlines and discusses the technique, the clinical utility of the aEEG and, most importantly, its predictive value in terms of short- and long-term outcome of preterm infants. First, technical aspects concerning the methodology and the assessment of the aEEG tracing are explained, with special focus on the potential aEEG signal confounders that interfere with a correct tracing evaluation. In particular, we provided data on the influence of sedatives of the aEEG tracing in newborn infants. Second, the prediction of neonatal and early childhood outcome of preterm infants is discussed in detail. Early recognition of preterm patients at particular risk for adverse outcome is important in order to tailor neonatal care and post-discharge intervention. Neuroprotective studies in preterm infants are being conducted to improve long-term outcome and robust biomarkers will help to guide such interventional strategies and to help parental counselling. This thesis demonstrates that changes in the aEEG background activity can predict short-term outcome in preterm infants. The maturational aspect of the early aEEG background tracing in preterm infants relates to structural brain maturation at term equivalent age as assessed qualitatively by magnetic resonance imaging. Additionally, a delay in the maturation of cyclic aEEG activity in the preterm newborn infant may be a sign of the development of a major brain lesion. This section ends with a review of the results of studies on the predictive value of aEEG for outcome at early childhood.

In conclusion the results of this thesis indicate that aEEG is a valuable neurophysiologic diagnostic tool for early continuous bedside monitoring of brain

function and aEEG background activity can predict short-term outcome in preterm infants. The assessment of the tracing evolution and the detection of sensitive markers of brain lesion during aEEG monitoring could prove critical for the selection and instruction of patients eligible for early neuroprotective therapies. Several clinical conditions and artefactual features may, however, alter the aEEG tracing and thus interfere with the interpretation and prognostic value of the aEEG. Training in the aEEG assessment and knowledge of the potential aEEG signal confounders is therefore needed to further improve the implementation of this promising neuromonitoring tool in the NICU.

## 2. List of abbreviations

aEEG:	Amplitude-integrated EEG
cMRI	Cranial magnetic resonance imaging
cPVL	Cystic periventricular leukomalacia
cUS	Cranial ultrasound scan
EEG:	Electroencephalogram
GA:	Gestational age
IVH:	Intraventricular haemorrhage
ND:	Neurodevelopmental disability
NICU	Neonatal intensive care unit
NPV	Negative predictive value
PMA:	Postmenstrual age*
PPV	Positive predictive value
PVHI	Periventricular haemorrhagic infarction
SWC:	Sleep-wake cycling

Note of the author on the terminology:

The term *postmenstrual age*, which refers to the time elapsed between the first day of the last menstrual period and birth (gestational age) plus the time elapsed after birth (postnatal or chronological age), will be used in this script. The term *postconceptional age* however, referring to the time elapsed between the day of conception and birth plus the time elapsed after birth, which has been used in some of the cited references, will not be used because for reasons of clarity. Both terms refer to a similar concept of age of a preterm infant, the first one however, is the term conventionally used (1).



### **3. Introduction**

While advances in perinatal care have resulted in improved survival rates of very preterm infants over the last three decades (2, 3), the incidence of major neonatal complications causing significant morbidity in this population remains unchanged (4). Thus, very preterm infants represent a growing patient population at risk for cerebral injury and thus ND (5-8). As a consequence, the focus in neonatal intensive care units (NICU) lies on the implementation of monitoring, treatment, and prevention of brain lesion. Further, clinicians' interest to get neurologic diagnostic and prognostic information already in early life period after birth is justified by the increasing amount of investigated neuroprotective agents and interventions (9, 10) that could find their threshold use in a near future. Prognosis of the outcome in preterms requires a broad approach and is based on neurological, neurophysiological, and neuroimaging findings (11). However, clinical neurological assessment of preterm infants in the early neonatal period is difficult since they are often clinically ill. Thus, detailed neurological examination often has to be delayed until they are clinically stable. Neuroimaging assessment in the NICU commonly includes serial cranial ultrasound (cUS) scans to detect cerebral injuries such as intraventricular haemorrhages (IVH), periventricular haemorrhagic infarction (PVHI), arterial stroke or white matter injury (12). Conventional and more advanced magnetic resonance imaging techniques such as diffusion tensor imaging and tractography, volumetry and morphometry provide more detailed information on the presence and extent of structural lesions of the white and grey matter compared to cUS (13, 14). However, this diagnostic procedure is difficult to perform during the very first days after birth in these critically ill preterm infants. Similarly, conventional EEG provides full spectrum information concerning the functional integrity of the brain, with relevant predictive value for outcome in preterm infants (15), but its feasibility 24 hours a day in the NICU for early neuronal function monitoring is limited due to restricted practicability and availability. The amplitude-integrated EEG (aEEG) however, is a user-friendly device, which can be easily used as a bedside neuromonitoring tool in the NICU. It provides immediate information on brain activity and its maturity, which is accessible also for EEG inexperienced clinicians. In the last 20 years aEEG began to play an ever-growing role in the evaluation of newborn infants admitted to a NICU. As a result, clinicians are increasingly faced with the interpretation of preterm aEEG. Little information is available however, concerning a) the evolution of maturational patterns of aEEG in

clinically stable preterms; b) the association between aEEG findings and cerebral lesions; and c) the association between aEEG findings and neurodevelopmental outcome. Knowledge on the evolution of maturational patterns of aEEG in preterms, and the factors influencing their trajectories may improve early detection of brain abnormalities and outcome prediction. That is of particular importance for the NICU clinician with respect to the direction of overall neonatal care and basis for neuroprotective intervention.

#### **4. Population under focus: very preterm infants (APPENDICES I, II)**

While preterm birth (before the end of the 37<sup>th</sup> gestational week) accounts for 10–13% of live births in high-income countries (16-18); very preterm birth (before the end of the 32<sup>nd</sup> gestational week) occurs approximately in 1% of live births (19), Swiss data being very similar to international one (20). Even though very preterm infants represent a small number of absolute live births, their need for intensive care medicine technology and the risk for long-term ND are of substantial public health relevance (21). In the last decades of the 20<sup>th</sup> century, their mortality rate constantly decreased, while neurodevelopmental morbidity remained almost unchanged (2, 3), which is still cause of major concern and explains the increased need for accurate long term outcome studies. Long-term outcome studies in the very preterm population group indicate higher vulnerability in a wide spectrum of developmental domains, ranging from somatic growth, learning abilities, behaviour, and motor performance to sensorial domains (5, 7, 8, 22-24). However, as design, prevalence of neonatal morbidities, characteristics of follow-up, and outcome variables vary substantially from study to study, a reliable comparison of their findings is difficult (25). The neonatal care policies concerning the care of preterm infants at borderline viability may further vary among different countries as well as within a country, which might also influence neonatal and long-term outcome figures. On overall, it is estimated that severe ND, usually defined as an aggregate comprising cerebral palsy, severe mental retardation, and severe visual or hearing impairment (23), reach a prevalence of approximately 10% in very preterm infants, while moderate-to-mild ND affects 30-50% of survivors. Moderate-to-mild deficits are more difficult to be detected during infancy and early childhood, but are also of major importance because of their high prevalence and because they may affect school performance and behaviour, and are cause of further burden for the families (26).

##### **4.1 Neonatal outcome of very preterm infants in Switzerland**

Recently, the Swiss Neonatal Network & Follow-Up Group (SNNFU), a health care professionals collaboration founded by the Swiss society of Neonatology, reported representative data on neonatal mortality and morbidities over a 12-years period, from 1996 to 2008 (20). They observed a significant increase of the birth rate of very preterm and very low birth-weight infants, i.e. with birth weight < 1500 grams, from 0.9% in 1996 to 1.1% in 2008, an overall stable mortality rate of 13% during the

observational period, and a significant increase of survival free of major complications, defined as major cerebral lesion, high staged retinopathy of prematurity, or bronchopulmonary dysplasia, from 67% to 72% (20). In a study on outcome of a Swiss national cohort of preterm infants born between the 24<sup>0/7</sup> and 27<sup>6/7</sup> gestational weeks, we observed that mortality was mainly predicted by low GA and low birth weight, while antenatal corticosteroids to induce fetal lung maturation had a strong protective effect (27) (Appendix I). The observed rates in mortality and morbidity were similar to the findings of other European groups (28, 29), while compared to recent United States (30) and Australian cohorts (31), mortality was slightly higher.

#### **4.2 Two years outcome of very preterm infants in Switzerland**

Based on a national prospective database, we reported on the overall outcome at 2 years of corrected age of in a Swiss cohort of extremely preterm infants, i.e. before the 28<sup>0/7</sup> gestational week, born over a nine-year period (2000 – 2008) (27) . In this recent and representative cohort study we demonstrate that although more than a third of infants still suffer from moderate or severe ND, the rate of survival without major neurologic sequelae has increased significantly over the first decade of this century. The incidence of severe ND was 11%, while 24% of infants survived with moderate ND. Interestingly, while adverse outcome, defined as death or severe ND, was predominantly dependant on GA, lower birth weight, and antenatal corticosteroids at birth, outcome at two years of age in children surviving the neonatal period was best predicted by the neonatal morbidities: major brain lesions as diagnosed by cUS, bronchopulmonary dysplasia, and retinopathy of prematurity (27). These findings are confirmed by other groups (32-34) and support the fact that the prognosis for preterm infants can substantially change during postnatal age (35) in function of the individual clinical course.

#### **4.3 Long-term outcome of former very preterms in young adulthood**

The outcome at young adult age in former very preterms has become object of increasing interest for many study groups during the last decade. Indeed, there is concern, whether and how prematurity affects late outcome, as defined by quality of life, and psychological functioning of this population. Previous studies report lower health utility scores in formerly extremely low birth weight (below 1000 grams at birth)

school-aged children and adolescents compared with peer controls (36). It seems however, that the effect of prematurity on quality of life diminishes over time (37) and that self-rated quality of life in young adulthood is generally surprisingly positive (38). Similarly, children and adults with chronic conditions and major handicap also perceived their quality of life close to normal (39, 40). The results of our study on 55 young adults born preterm in Switzerland during the early 1980s with a birth weight below 1000 grams demonstrated that their self-perceived health status and mental health was overall satisfying (41) (Appendix II). The comparison with the community norms revealed however, that not all domains of quality of life are equally adjusted, the socio-emotional domain being specially affected (41). These data however, may not be representatives for the generations of preterm infants born during the last three decades, when perinatal care improved relevantly.

While preterm birth has been associated with an increased risk of attention deficit and hyperactivity disorder (42) as well as of emotional disorders and autism (43) at adolescent age, it has been recently reported that preterm birth constitutes a single independent risk factor for a range of psychiatric diagnoses also at young adult age (44, 45). These findings are of major importance because not only cognitive and motor deficit but also psychological and behavioural disturbances may affect the social integration of the former preterm born individuals (26).

## **5. Amplitude-integrated electroencephalogram (aEEG)**

### **5.1 Generals on aEEG**

Until the late 1990's continuous monitoring of the physiological parameters of a NICU's patient was focussed and limited to heart rate, blood pressure, oxygen saturation, and body temperature. In the last 20 years however, continuous monitoring of the brain function by aEEG was integrated into the routine care and became a daily part of clinical surveillance of sick newborn infants in an increasing number of NICUs. The reasons of its rapid diffusion are to be found in its feasibility and easier interpretability compared to those of conventional EEG. Additional contributors are its good correlation with conventional EEG data, and, perhaps more important, its high sensitivity for predicting outcome during the first hours after birth in full-term newborn infants with neonatal encephalopathy following perinatal asphyxia (46). The constantly growing interest in long-term monitoring of the brain activity by aEEG in newborn infants follows the increasing knowledge and application of neuroprotective interventions in this patient population.

#### **5.1.1 aEEG history**

aEEG is a non-invasive method of brain activity monitoring, used in the intensive care of newborn infants since 1980. The method is however not new. A device for continuous EEG trend monitoring has been firstly developed with the name of 'cerebral function monitoring' by Dr. Douglas Maynard in the late 1960's in the UK (47, 48). Shortly later, his colleague Dr. Pamela Prior investigated its first clinical application on adult patients with status epilepticus, after cardiac arrest, and during anaesthesia. The term 'cerebral function monitoring' has been substituted by the term 'amplitude-integrated EEG', actually preferred in order to denote the method rather than specific equipment. In the late 1970's, brain function monitoring by aEEG first focused on normal tracing in term and late-preterm newborn infants, as well as on the detection of clinical silent seizures (49-51).

#### **5.1.2 aEEG method**

aEEG is derived from a raw EEG signal. The first single channel aEEG devices usually recorded the EEG signal from a pair of biparietal electrodes placed in correspondence of P3 and P4 according to the EEG international 20-10 system, ground Fz (52). Thin subdermal needles-, disc hydrogel-, or cup electrodes are used.

While the information on brain activity is reduced to a trans-cerebral trace, and does not allow detection of hemispheric asymmetry, most of commercial aEEG devices offer nowadays the possibility to monitor brain activity from two centro-parietal channels placed upon both brain hemispheres, i.e. in correspondence of C3-P3 and C4-P4. That is of clinical significance, especially in infants with unilateral brain injury. The physiologic basis and aEEG engineering have been described in depth elsewhere (53), however following steps are to retain:

- The raw EEG signal is amplified and passed through an asymmetrical band pass filter. This process strongly attenuates activity below 2 Hz and above 15 Hz and consequently minimizes artefacts from muscle activity, sweating or other electrical interferences.

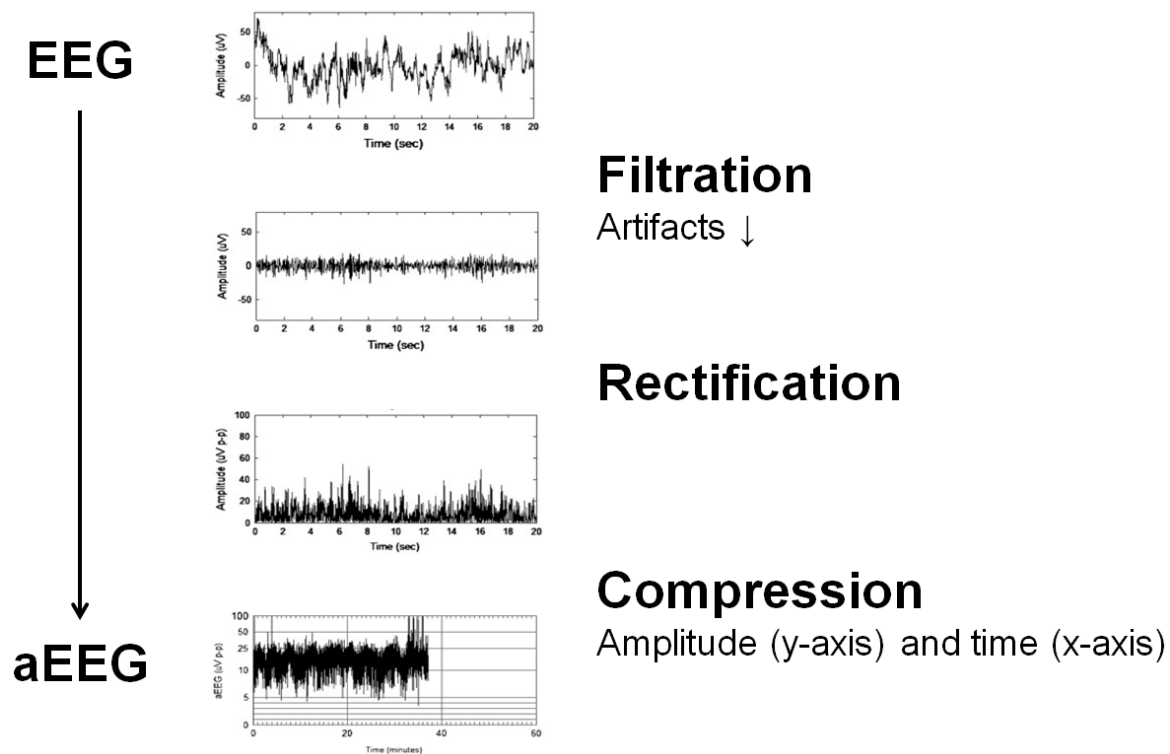
- The signal is then rectified. After this process, the monitor will display only positive amplitude voltage which reflects the peak-to-peak amplitude variation in the raw EEG. Thus, focus of the aEEG assessment becomes the trend of the amplitude variations of the raw EEG, while any analysis of grapho-elements or frequencies results beyond the bounds of possibility.

- Further, the amplitude of the signal is semi-logarithmic compressed. The analysis of the lower amplitude ranges, linearly displayed until 10  $\mu$ V on the y-axis of the monitor, is hence enhanced. That is particularly important in the voltage range below 5  $\mu$ V.

- Finally the signal is time compressed and displayed on the x-axis at slow speed (1 hour per 6 cm).

Figure 1 schematically displays the main steps of the aEEG signal processing.

**Figure 1:** Main steps of the aEEG signal processing (modified after El-Dib et al., 2009 (54)).



## 5.2 Rationale for the use of aEEG in preterm infants

Information about the presence and extent of a brain lesion of newborn infants is preferably obtained within the first hours after its development. This is not only important to direct overall care and inform parents about their infant's current condition, but also to obtain predictive information about further outcome. Early selection of patients with neurophysiological monitoring by aEEG could also be useful for targeted diagnostic intervention such as neuroimaging or future neuroprotective intervention. aEEG helps to guide management of critically ill patients as it enables early identification of acute brain injury in preterm infants providing a continuous recording of the functional brain integrity around-the-clock immediately after admission in the NICU (55). Because of long periods of registration, aEEG is particularly useful to evaluate changes in the trend of the background pattern of the brain cortical activity over time and to detect the occurrence of silent or subclinical seizures. While video-conventional EEG remains the gold standard of neonatal electroencephalographic activity study, its feasibility in the NICU patient is limited. For a standard neonatal EEG, 9 electrodes are used to



produce 14 bipolar derivations together with channels for eye movement, muscle activity, and electrocardiogram. The standard duration of a conventional EEG recording lasts for approximately 30 minutes (56). This is very demanding if applied on an extremely and instable preterm newborn infant.

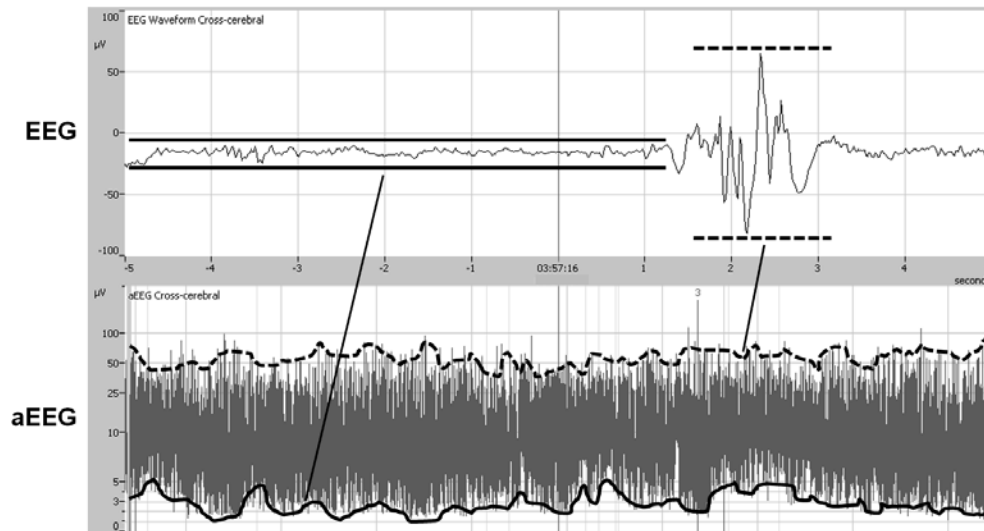
In the last twenty years, a number of single- or bi-channel aEEG studies with simultaneous multichannel standard EEG were performed, demonstrating a very high concordance between the two techniques with respect to both the background pattern and the ictal activity in the sick newborn infant (46, 57-61). Thanks to long-term brain function monitoring with aEEG, electrographic seizures are easier to detect and the efficacy of anticonvulsant therapies can be evaluated objectively during the monitoring period (55).

### **5.3 aEEG tracing assessment**

Assessment of the aEEG focusses on the analysis of the background pattern, of the presence (or time of occurrence) and character of sleep-wake cycling (SWC) and finally of the presence of seizure activity. Basically, aEEG has been created as a bedside, analogical monitoring tool for visual pattern evaluation of the brain function. The development of new aEEG devices, more sophisticated and of digital nature, made it possible for the clinicians and researchers to perform quantitative analysis of aEEG parameters and of its correspondent EEG signal. The quantitative analysis of the maximum and minimum aEEG amplitudes helps to better define the bandwidth of the aEEG signal, which reflects the variations in the minimum and maximum EEG amplitudes. The maximum aEEG amplitude, or 'upper margin' of the aEEG bandwidth, is defined by the peak-to-peak amplitude of the EEG bursts, while the minimum aEEG amplitude, or 'lower margin' of the aEEG bandwidth, is defined by the peak-to-peak amplitude of the interburst EEG period (62) (see figure 2).

The discontinuous EEG activity is quantified by the assessment of the percentage of discontinuity, the interburst interval [i.e. the period of so-called flat EEG (suppression), between two bursts of activity (periods of slow waves of high amplitude)], the burst frequency or the burst duration (63). Similarly, power spectral analysis of the raw EEG signal displays the quality of the electrocortical background activity.

**Figure 2:** Maximum (dotted line) and minimum (continuous line) aEEG amplitudes reflect the peak-to-peak amplitude variation during a cluster of activation and during the period between two clusters in the raw EEG, respectively (according to Rosèn, 2006 (62)).



### 5.3.1. aEEG background pattern

Two different methods for the classification of the aEEG background pattern are defined and frequently used (see figure 3).

#### 5.3.1.1 The pattern classification

In 2006, Hellström-Westas and associates published a aEEG trace classification (64) based on the visual perception of the dominating five different background patterns which correspond to the relative electrocortical activity:

- 1) Continuous voltage pattern: background activity with minimum amplitude around (5 to) 7 to 10  $\mu\text{V}$  and maximum amplitude of 10 to 25 (to 50)  $\mu\text{V}$
- 2) Discontinuous voltage pattern: background activity with minimum amplitude variable, but  $< 5 \mu\text{V}$ , and maximum amplitude  $> 10 \mu\text{V}$
- 3) Burst-suppression: discontinuous background with minimum amplitude without variability at 0 to 1 (2)  $\mu\text{V}$  (suppression) and bursts with amplitude  $> 25 \mu\text{V}$ . 'Burst suppression +' denotes a burst density  $\geq 100$  bursts per hour, while 'burst suppression -' means a burst density  $< 100$  bursts per hour.
- 4) Low voltage: continuous background pattern of very low voltage (around or  $< 5 \mu\text{V}$ ).

5) Inactive, flat: primarily inactive (isoelectric tracing) background  $< 5 \mu\text{V}$ .

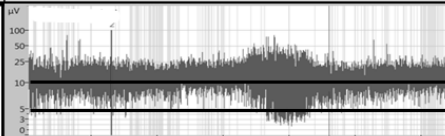
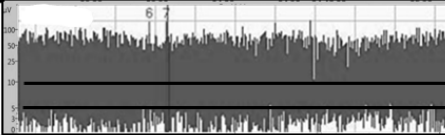
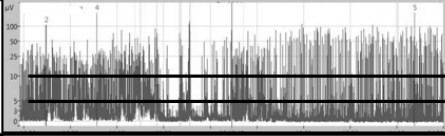
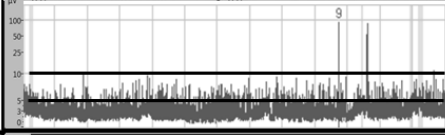
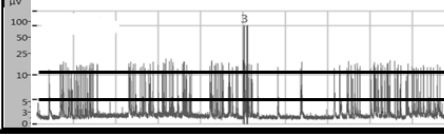
#### **5.3.1.2 The voltage classification**

aEEG background can also be described in function of the voltage of the measured upper and lower aEEG amplitude. This classification system, published by Al Naqeeb and associates in 1999 (65), is based on the aEEG voltage range and distinguishes basically three backgrounds:

- 1) Normal amplitude: lower margin of aEEG bandwidth  $> 5 \mu\text{V}$  and upper margin of aEEG bandwidth  $> 10 \mu\text{V}$ ;
- 2) Moderately abnormal amplitude: lower margin of aEEG bandwidth  $\leq 5 \mu\text{V}$  and upper margin of aEEG bandwidth  $> 10 \mu\text{V}$ ; and
- 3) Severely abnormal amplitude: lower margin of aEEG bandwidth  $< 5 \mu\text{V}$  and upper margin of aEEG bandwidth  $< 10 \mu\text{V}$ .

When the voltage classification system is used, care should be taken in case of an artefactual drift, i.e. a rise of the baseline. This can be frequently seen in severely depressed background pattern if extra-cranial electrical interferences occur, for example electrocardiography (60).

**Figure 3:** The assessment of the aEEG consists in the recognition of the dominant of 5 backgrounds according to a pattern or a voltage classification

Voltage Classification Al Naqeeb et al., 1999	Pattern Classification Hellström-Westas et al., 2006		
<b>Normal</b> Lower amplitude margin > 5 $\mu$ Volt Upper amplitude margin > 10 $\mu$ Volt	<b>Continuous voltage</b>		Normal trace
<b>Moderately Abnormal</b> Lower amplitude margin $\leq 5$ $\mu$ Volt Upper amplitude margin > 10 $\mu$ Volt	<b>Discontinuous voltage</b>		Abnormal in the full-term but normal in the preterm newborn
	<b>Burst suppression</b>		Abnormal trace
<b>Severely Abnormal</b> Lower amplitude margin < 5 $\mu$ Volt Upper amplitude margin < 10 $\mu$ Volt	<b>Low voltage</b>		
	<b>Flat trace</b>		

Modified after (66) on own examples of aEEG tracings.

### 5.3.2 Sleep-wake cycling

The observation of the aEEG tracing in a clinical stable newborn infant allows the recognition of a regular cyclic change in the background pattern. In the neurologically healthy term newborn infant this cyclic variation is typically smooth and sinusoidal, characterises mostly the minimum amplitude, and is called SWC. The broader bandwidth represents discontinuous background activity during quiet sleep (tracé alternant EEG in term infants), and the more narrow bandwidth corresponds to the more continuous activity during wakefulness and active sleep.

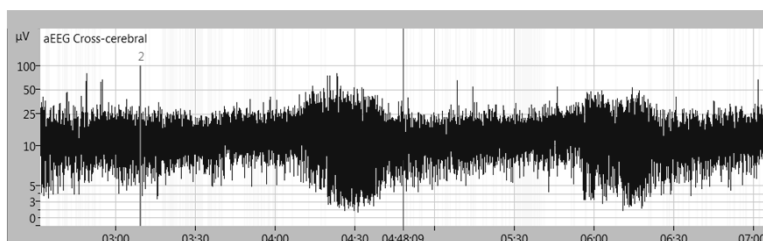
According to Hellström-Westas and associates, aEEG SWC is classified as developed, imminent or immature, and absent SWC (64). Noteworthy however, the distinction of the transitions from sleeping and waking states in the child is not possible only through neurophysiological monitoring, but also through clinical (physiological and behavioural) observation, which is not seen in the aEEG. For that reason, some authors tend to define the aEEG background pattern variation in

newborn infant with the more neutral term of aEEG ‘cycling’ (67, 68) or ‘cyclicity’ (69-72), especially in the preterm infant. This is of relevance as SWC is less defined in more immature and more instable newborn patients. Figure 4 depicts examples of the three described SWC features. In this script the mention “cycling activity” will be preferred.

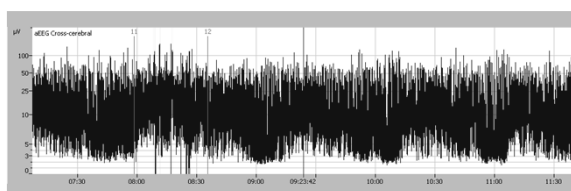
- 1) Developed cycling activity (SWC, in the original publication): clearly identifiable sinusoidal variations between discontinuous and more continuous background activity are observed, with cycle duration  $\geq 20$  min.
- 2) Imminent/immature cycling activity (SWC, in the original publication): some, but not fully developed cycling activity of the lower amplitude is observed, but not developed as compared with normative GA representative data.
- 3) No cycling activity (SWC, in the original publication).

**Figure 4:** According to the Hellström-Westas and associates (64) aEEG cycling activity (SWC, in the original publication) is classified in three main forms: a) developed, b) imminent/immature, c) absent cycling activity.

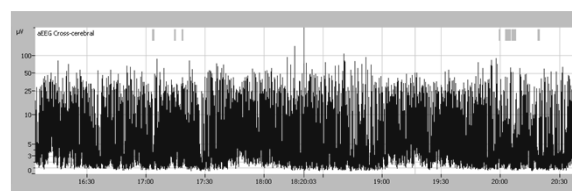
#### a) Developed



#### b) Imminent / Immature



#### c) Absent



### 5.3.3 Seizures

Seizures occur in approximately 50 per 1000 live preterm births, while in full term newborn infants, they occur in 1-3.5 per 1000 live births (73). The more immature or clinically instable the infant, the higher the probability of developing seizure activity

(74). However, Murray and associates observed in a video-conventional EEG study that only a minority of newborn infants show overt clinical signs of seizures, while in a majority of newborn infants, the clinical manifestations of electroencephalographic seizures are under recognized or misinterpreted even by experienced NICU staff (75, 76). Subclinical seizure can be referred to the phenomenon of electroclinical dissociation or “uncoupling”, characterised by reduced or absent clinical features during an ictal crisis associated with EEG seizure pattern (77-79). This phenomenon can be even more often observed in the immature and sick newborn infant after administration of anti-epileptic drugs (75, 78). Data about the incidence of subclinical seizures in the preterm newborn infant are still scarce. The application of aEEG for long-term monitoring of the brain activity allows the detection of this phenomenon and the differentiation of several seizure-associated behavioural patterns (i.e. oxygen desaturations or apneas) from non-ictal episodes (i.e. respiratory insufficiency). In the aEEG, ictal activity is seen as an abrupt rise in the minimum amplitude often accompanied by a simultaneous rise in the maximum amplitude. A short period of decreased amplitudes often follows this sudden pattern change (see figure 5). In the simultaneous review of the raw EEG attention should be paid to the typical features of seizure activity, with a gradual build-up and then decline in frequency and amplitude of repetitive stereotypical spikes or sharp-waves of activity with duration of at least 10 sec.

According to Hellström-Westas and associates (64) seizure activity in the aEEG is classified as follows:

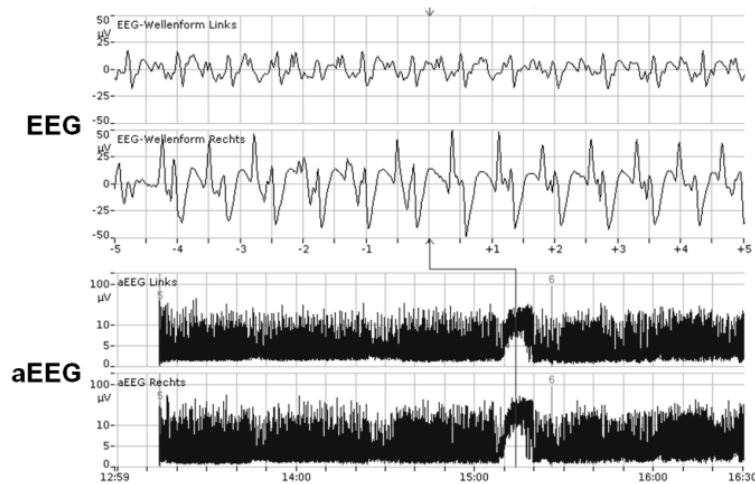
- 1) Single seizure: a solitary seizure is observed.
- 2) Repetitive seizures: single seizures appear more frequently than at 30-minute intervals.
- 3) Status epilepticus: a continuously ongoing seizure activity for > 30 minutes is observed.

It has been questioned whether single- or two-channel aEEG is a sufficiently reliable tool to detect epileptic activity. Because of the aEEG signal processing method, where both time and amplitude are compressed, and the limited number of electrodes used, focal seizure episodes of low-amplitude and short duration (< 30 seconds) are hardly recognizable on aEEG (61). Furthermore, it can be difficult to distinguish between seizures and artefacts, for example due to handling of the infant or other electrical interferences. However, some aEEG/EEG studies have

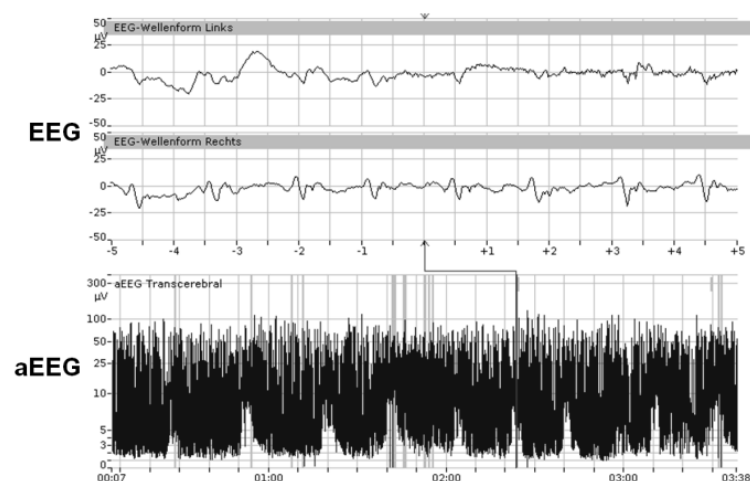
demonstrated acceptable sensitivity for the detection of electrographic seizures, the C4–C3 derivation providing the best identification rate (75, 80, 81). The use of a two-channel aEEG device and the simultaneous review of the raw EEG signal is therefore preferred for electrographic seizures detection in high risk newborn infants, particularly in the case of unilateral brain lesions. In case of difficult and doubtful aEEG traces with suspected seizures, it is suggested to perform video-conventional EEG exam as gold standard diagnostic method.

**Figure 5:** aEEG tracings with corresponding raw EEG signal with examples of a) single, b) repetitive seizure activity, and of c) status epilepticus.

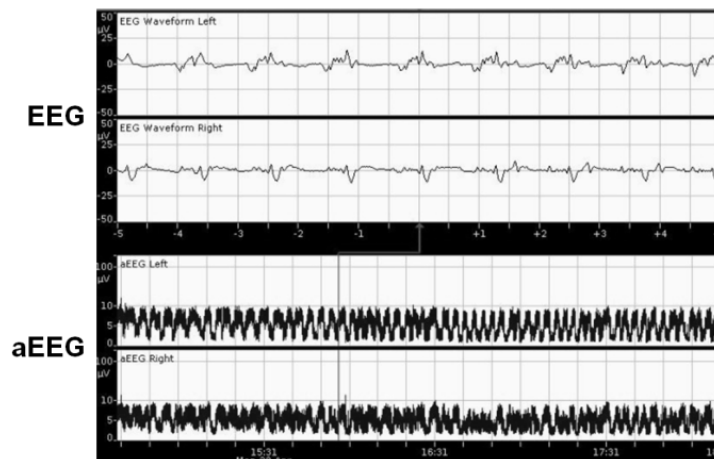
#### 5.a) Single seizure



#### 5.b) Repetitive seizures



### 5.c) Status epilepticus



(BrainZ Instruments LTD, © 2004)

## 5.4 aEEG interpretation caveats (APPENDIX III)

Pitfalls in the interpretation of the aEEG background pattern have been well described in the last years (60, 61, 80-88). Basically, one has to be aware of 3 fundamental caveats when assessing cortical activity of a preterm infant with aEEG. Noteworthy, beneath technical aspects which mainly concern the assessment equipment, also general clinical conditions and care of the NICU patient (63, 64) may affect the aEEG tracing. As a result, factors which may cause extra-cortical and/or cortical aEEG tracing modifications must be considered to avoid misinterpretation (Natalucci et al, submitted 2013). Evidences concerning the influence of other factors on aEEG activity in the preterm need to be confirmed in larger study populations.

### 5.4.1 Caveat 1: electrodes location

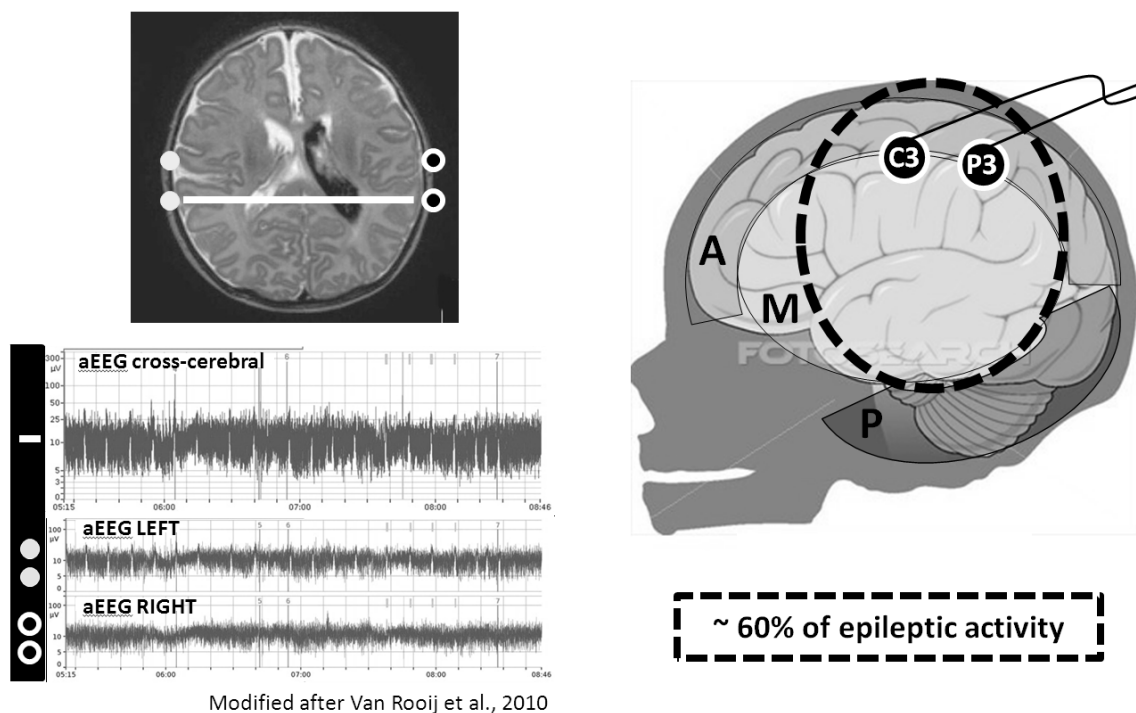
Recognition of the regional limitations of the use of such a simplified form of electroencephalography is important. While the “one-channel” aEEG perspective, i.e. electrodes P3-P4, provides general information about the brain function, with “two-channel” mode, i.e. C3-P3 / C4-P4, it is possible to identify elementary signs of asymmetry in the cortical activity and eventually to localize the side of the injured region. Please see figure 6, where seizures are localized on the left side in the two-channel aEEG tracing in an infant who developed a large left IVH (82). However, even if the optimal C3-P3 / C4-P4 electrode location allows the surveillance of a cortical area where about 60% of epileptic activity occurs in the newborn brain, it is still not possible to detect all seizures, nor their temporal development. Importantly, because of the aEEG signal processing where both time and amplitude are



compressed, the examiner will not be able to detect seizure episodes of short duration or low amplitude without reviewing the simultaneous raw EEG sequence.

**Figure 6:** Regional limitations of single- and two-channels aEEG tracing. *Right:* T2-weighted axial MR sequence showing a large left-sided IVH; repetitive seizures are observed on the single-channel (trans-cerebral, P3/P4) aEEG tracing of the same patient, but localised on the left side through the two-channel aEEG tracing. This case described in a recent Dutch publication has been chosen as example (82).

*Left:* the C3/P3 electrodes location covers a watershed region between the perfusion areas of the anterior and middle cerebral arteries, and covers a brain cortical area where approximately 60% (89-91) of all seizure activity can take place in a newborn brain.



A, M, P, perfusion area of the anterior, middle, and posterior brain artery, respectively; C3/P3, electrodes location. Modified after SA302011 LifeART Medical Illustrations Photograph Royalty Free ([www.fotosearch.com](http://www.fotosearch.com)).

Electrode scalp location does not only determine the sensitivity of aEEG to detect seizure activity (81, 92) but seems also to significantly influence both the upper and the lower aEEG amplitudes, trans-central (C3-C4) aEEG values from term infants being significantly higher than trans-parietal (P3-P4) (87). Similarly, increasing inter-electrode distance increases quantitative aEEG measures (87).

### 5.4.2 Caveat 2: aEEG artefacts

Caution is recommended when assessing aEEG because artefacts contribute to the tracing rendering its readability problematic. aEEG artefacts are common during long-term recording and can be derived from mechanical as well as electrical interferences. The most frequently observed sources of artefacts are listed in table 1. Hagmann and associates reported that artefacts occurred in 12% of the 200 hours of aEEG recording randomly selected from a cohort of term newborn infants with neonatal encephalopathy following perinatal asphyxia (83). The ratio of occurrence of artefacts derived from movement and caused by electrical interferences was of about 1:1. That may lead to erroneous classification of the aEEG trace. Similarly, Suk and associates observed that artefacts contribute substantially to the aEEG tracing also in preterm infants (84).

Because of the relative frequent occurrence of artefacts in aEEG it is of primary importance to review real time and retrospectively both aEEG and its deriving raw EEG (61, 85, 86).

**Table 1: The most frequent artefacts and correspondent effect on aEEG tracing**

Artefact source	Effect on aEEG tracing
High-frequency oscillation Electrocardiogram	Drifting of the lower bandwidth margin. Low voltage patterns of effective <1-2 $\mu$ V are artificially displayed with higher lower bandwidth margin.
Electromyogram Electrode padding	Drifting of the lower and higher bandwidth margin. aEEG seizure-like features are artificially produced.
Electrode positioning	The measured voltage is function of the electrode distance. Electric bridges, caused by touching electrodes, result in an artificial isoelectric voltage.
Application techniques	Low impedance values, i.e. good EEG signal recording, results from a correct and standard electrodes application.

As gold standard method, conventional EEG plays a clarifying role in the case of difficult or impossible interpretation, even if it allows only a momentary recording. The use of intradermal needles-electrodes and very low (0.1 to 5 kOhm) signal

impedance measurements over time allow high reduction of artefacts (60). In a recent study on the engineering aspects of the aEEG however, Quigg and associates demonstrated that, while high impedance mismatch distorts EEG and aEEG it does not significantly changes quantified aEEG measurement (87).

### **5.4.3 Caveat 3: clinical confounders**

Another source of confounders is represented by the use of specific medications during aEEG monitoring (such as sedatives) or neonatal clinical variables (such as arterial hypotension) which are known to influence cortical activity and aEEG tracing.

#### **5.4.3.1 Effect of medications on aEEG**

##### *Sedative, analgesic and antiepileptic drugs*

Central sedatives and analgesics, and antiepileptic drugs may lead to a transient suppression of cerebral activity (63, 88, 93-97), especially in sick infants with otherwise severely compromised cerebral function, and in very immature newborn infants in their early days of life. Morphine induces a suppression of the aEEG background tracing, when given in bolus injection (up to 100 µg/kg) or continuous injection (up to 12 µg/kg/h) in the very preterm newborn infant (93, 95) (Natalucci et al, submitted 2013). Niemmarkt and associates published that a patient with moderate perinatal asphyxia, who received an accidental overdose (5000 µg/kg) of morphine developed a change of the background from continuous to discontinuous pattern (98). In contrast, we observed that intravascular continuous morphine administration (up to 40 µg/kg/h) did not induce any relevant aEEG change in cardiac newborn patients with GA above 32 weeks in the early post-surgery period (97) (Appendix III). We and others could demonstrate however, that bolus injections of stronger opioids than morphine, as fentanyl (up to 10 µg/kg) or sufentanyl (up to 0.5 µg/kg) induce severe suppression or even a transient flattening of the aEEG/EEG tracing in full-term as well preterm newborn infants (97, 99). Our experience at the division of neonatology in Zurich, and that of other groups (64, 93, 95), is that a loading dose of phenobarbitone (up to 20 mg/kg) may result in a moderate depression of aEEG background activity in preterm. Similarly, newborn infants requiring bolus injection of midazolam, diazepam, or lorazepam (all up to 0.1mg/kg) show a transient depression of the aEEG activity, which is less marked in the full-term infants (64, 97, 100). However, both phenobarbitone and midazolam can induce a profound suppression of

the aEEG activity in the full-term newborn infants with neonatal encephalopathy following perinatal asphyxia, which may persist for a considerable period (101). The influences of lidocaine, given as a continuous injection (up to 4 mg/kg/h) for treatment of recurrent seizures often results in a discontinuous or burst suppression aEEG pattern (96, 100).

#### *Caffeine and aminophylline*

Arousing medications such as caffeine (loading dose of 10 mg/kg) (102) or aminophylline (loading dose of 5 mg/kg) (103), used for prevention and treatment of apneas, are also known to influence EEG/aEEG activity, both having been associated with an increase in aEEG background continuity. These findings are not in agreement with ours, where caffeine, given at a higher loading dose of 20 mg/kg, did not influence the aEEG tracing of 96 neurologically healthy preterms (Natalucci et al, submitted 2013).

#### *Indomethacin*

Data concerning the influence of indomethacin, given for closure of patent ductus arteriosus, is poor. In our experience indomethacin, given in a short duration infusion of 0.5 to 1 mg/kg, did not influence significantly the course of the aEEG recording over the first four days of life (Natalucci et al, submitted 2013). This is in agreement with Flisberg and associates who reported in a small group of preterm infants that indomethacin in similar doses as given in our centre does not affect cerebral function as evaluated by quantitative EEG (104). The aEEG analysis of the effect of indomethacin and of a haemodynamic relevant patent ductus arteriosus would be of benefit as both factors influence independently cerebral haemodynamic (105, 106).

#### *Surfactant*

Finally, it has been observed that in preterm infants, surfactant administration may result in a short transient aEEG depression parallel to a rise in cerebral blood volume as measured with near-infrared spectroscopy (107-109). The mechanism underlying the cortical activity suppression after surfactant therapy is object of controversy. In some studies infants with IVH were not excluded nor infants under phenobarbitone or sedative medication. Opioids sedation, as already mentioned, and intubation also alter cerebral function in the preterm infants (63, 110). An increase in cerebral blood volume has been observed after endotracheal surfactant instillation independently from major changes in the blood pressure or gases' partial pressures (109) and with no negative effects on cerebral oxygen delivery and -extraction (108). That increase

in cerebral blood volume seems to be related to the volume of surfactant instilled (108, 111). That suggests that the volume of endotracheal instilled fluid may also play a role with respect to possible changes in cerebral oxygenation shortly after surfactant administration (111). In our experience we did not observe any relevant influence of surfactant administration on the aEEG tracing in preterm infants. Our population's characteristics and clinical setting are however, different from those of the studies cited above.

#### **5.4.3.2 Effect of perinatal and neonatal factors on the aEEG tracing**

##### *Chorioamnionitis*

Chorioamnionitis negatively affect the aEEG background of the very preterm infants early after birth. While the amplitudes of early aEEG are negatively associated with the presence of a clinically and pathohistologically defined chorioamnionitis (Natalucci et al, submitted 2013), early aEEG/EEG depression quantified by interburst interval is positively associated with the umbilical cord TNF- $\alpha$  (112).

##### *Small for gestational age*

We observed that preterm infants born small for GA, i.e. with birth weight below the 10<sup>th</sup> percentile for GA, tend to display higher maximum aEEG amplitude during the first four days after birth (Natalucci et al, submitted 2013). That might reflect disorganised and dysmature pattern on conventional EEG with higher amplitude, characteristic of chronic stage abnormalities (113) in these growth retarded infants.

##### *Clinical instability*

It has been demonstrated by a Dutch group that severe illness as measured by the 'neonatal acute physiology score, SNAP-II', and low blood pressure have a suppressive influence on aEEG in preterm patients (114). Severe hypoglycaemia (<1.0 mmol) has been described in a pilot study to cause transient depression of aEEG background (115), while mild hypoglycaemia seems to relate to no (116) or only (117) subtle changes in the EEG amplitude. A case of decreased aEEG background activity during neonatal pneumothorax has been reported in the past (115).

##### *Unconjugated hyperbilirubinaemia*

Unconjugated hyperbilirubinaemia is known to acutely expose preterm infants to further neurodevelopmental risk. Although EEG amplitude is negatively related to

bilirubin levels (118), the observed aEEG bilirubin-related changes are modest, transient and delayed from 1 to 2 weeks after the measured event.

#### *NICU interventions*

Music has also been shown to influence the aEEG pattern in neurologically healthy late-preterm and term newborn infants, where a trend to more mature cycling aEEG activity was observed compared to not music-exposed controls (119). That finding is of relevance considering that music is being increasingly used in the context of neurodevelopmental care in NICUs, as a valuable resource to reduce stress and increase physiological stability (120).

### **5.5 aEEG in preterm infants**

The interpretation of the aEEG of the immature brain of preterm infants is additionally more problematic than in term infants (a) because of its own specific background and cycling character and (b) because it is apparently influenced by brain maturity, which can be defined by the GA, and by the time of extra-uterine brain exposition, defined as the postnatal age.

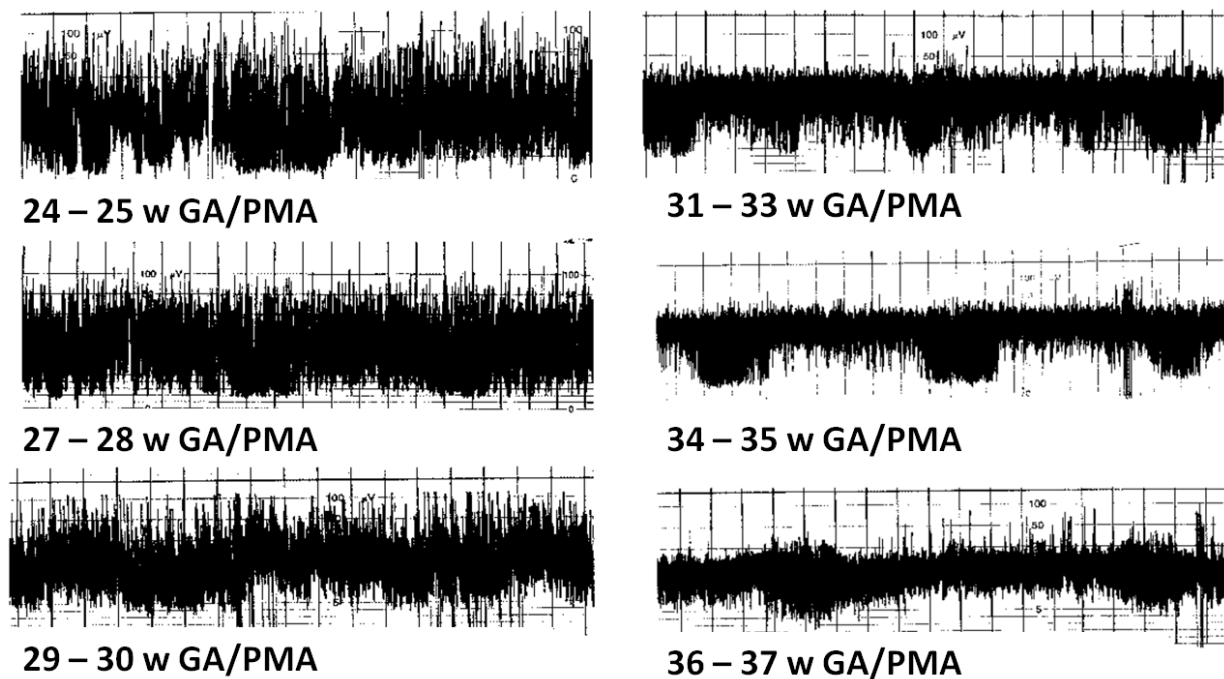
a) The aEEG background activity is primarily discontinuous in the very preterm infants, where this pattern is normal, and develops to a predominantly continuous aEEG background pattern until the 35-36<sup>th</sup> postmenstrual week. It is important to distinguish between the normal discontinuous aEEG (in the EEG this is called 'tracé discontinu'), and the abnormal burst suppression pattern (refer to figure 3). While the first is characterized by variable, lower aEEG amplitude activity of 0 to 5  $\mu$ V, the latter shows a straight, almost not variable lower aEEG amplitude of 0 to 1  $\mu$ V, corresponding to the inactive suppression period observed in the conventional EEG. Cyclic aEEG bandwidth variations suggestive of immature SWC emerge in stable, neurologically healthy preterm infants as soon as the 25<sup>th</sup> to 26<sup>th</sup> week of gestation is reached, and progressively develop until being definitely recognized at the 31<sup>st</sup> to 32<sup>nd</sup> postmenstrual week (68, 88, 121, 122) (Natalucci et al, submitted 2013) (see figure 7).

b) The normal aEEG background of preterm infants changes with GA, which may define cerebral maturation at birth, and with postnatal age, which may define the time of extra-uterine brain exposition (57, 68, 123-125) (Natalucci et al, submitted 2013). As a result, while assessing preterm aEEG it is essential to be aware of both time factors in order to define normality in function of the infant maturity.

Normative values of aEEGs are of relevant clinical utility for the identification of maturational brain disturbances or dysfunctions in this population group. However, age-adequate aEEG norms concerning qualitative or quantitative characteristics in preterm infants are scarce. Based on the results of previous studies published between 1984 and 2004, Hellström-Westas and associates summarised normal aEEG tracing characteristics at different GA (64) shown in table 2.

Olischar and associates published in 2004 reference values for aEEG in clinically stable and neurologically normal preterm infants with GA below 30 weeks during their first two weeks of life (123). They objectivize an increase in the continuity of the aEEG background in function of GA, reporting the percentages of the different background patterns and the percentiles as reference for preterm infants below 30 week GA. However, they did not describe the postnatal development of the aEEG tracings.

**Figure 7:** aEEG background pattern changes in function of brain maturity as defined by the postmenstrual age. The cycling character of the aEEG tracing emerges with increasing GA/PMA. Modified after (68).



The norms provided by Zhang and associates in 2011, ranging from 30 to 55 weeks PMA, were based on the largest dataset published to date (125). In agreement with

other groups (95, 123, 126) (Natalucci et al, submitted 2013) they showed that continuity, and both the lower and upper aEEG amplitudes, as well as the aEEG bandwidth develop with increasing PMA (125). They did not report however if those norms are influenced by the GA. We and others reported that aEEG developmental trajectories change over the postnatal period in function of GA (77, 95) (Natalucci et al, submitted 2013).

**Table 2: Normal aEEG characteristics in preterm infants at different GA/PMA. Modified after (64).**

	Qualitative aEEG characteristics		Quantitative aEEG/EEG characteristics		
GA or PMA (weeks)	Background <sup>1</sup>	Cycling activity	aEEG minimum amplitude (µV)	aEEG maximum amplitude (µV)	Bursts/hour
24 – 25	D	Imminent/immature	2 – 5	25 – 50 (100)	> 100
26 – 27	D	Imminent/immature	2 – 5	25 – 50 (100)	> 100
28 – 29	D / (C)	Imminent/immature, Developed	2 – 5	25 – 30	> 100
30 – 31	C / (D)	Developed	2 – 6	20 – 30	> 100
32 – 33	C / D in QS	Developed	2 – 6	20 – 30	> 100
34 – 35	C / D in QS	Developed	3 – 7	15 – 25	> 100
36 – 37	C / D in QS	Developed	4 – 8	17 – 35	> 100

Dominating aEEG background pattern; D, discontinuous background pattern; C, continuous background pattern; QS. quiet sleep

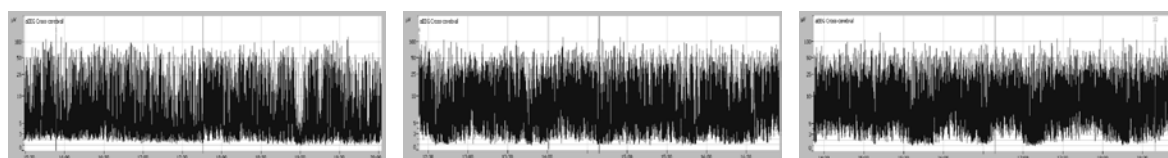
According to that observation, it seems that, for a given PMA, infants with lower GA might have a more continuous cerebral activity than others, which still is of unknown predictive value (see figure 8). External stimuli experienced by the preterm infant during the stay in NICU might be a cause of the “accelerated” extrauterine development of cortical activity. Thus, while defining the norms for measurable aEEG parameters in the preterm infant it is important to simultaneously consider both GA and the actual postnatal age of the patient at which the aEEG assessment has been done.

Burdjalov and associates (68) developed a valid scoring system allowing the evaluation of the maturity level of aEEG tracings of preterm infants. This score, based on visual qualitative and quantitative measurements of four aEEG components, allowed them to demonstrate that the brain maturation of newborn



infants can be followed and quantified by aEEG monitoring. Following aEEG aspects are analysed: a) the ‘continuity’ of aEEG trace; b) the ‘cycling’ character of aEEG trace; c) the average ‘minimum aEEG amplitude’ (or the lower margin of the aEEG bandwidth); and d) the aEEG ‘bandwidth’. Each component is scored and individual values are summed to determine a ‘maturity total score’ for the aEEG tracing, ranging from 0 to 13, the lower the score the more immature the brain activity. The highest total scores are reached at 35 to 36 weeks of postconceptional age.

**Figure 8:** aEEG tracings of a preterm newborn boy of the 26 2/7 week GA at 1, 2 and 4 days after birth. Qualitatively, the tracing characteristics are scored 2, 6, and 8 according to (68), respectively. That reflects maturity total scores which are typical for GA/PMA 24-25, 27-28, and 29-30 weeks, respectively.



1. day after birth	2. day after birth	3. day after birth
Maturity total score = 2/13	Maturity total score = 6/13	Maturity total score = 8/13
Continuity = 0/2	Continuity = 1/2	Continuity = 2/2
Cycling = 0/5	Cycling = 1/5	Cycling = 2/5

A limitation in all efforts aimed to define normal values for aEEG tracing in the preterm infant is represented by the fact that qualitative assessments (i.e. scores) may imply a certain degree of subjectivity which may affect inter-rater agreement.

## 5.6 Prognostic value of aEEG in preterm infants (APPENDICES IV, V)

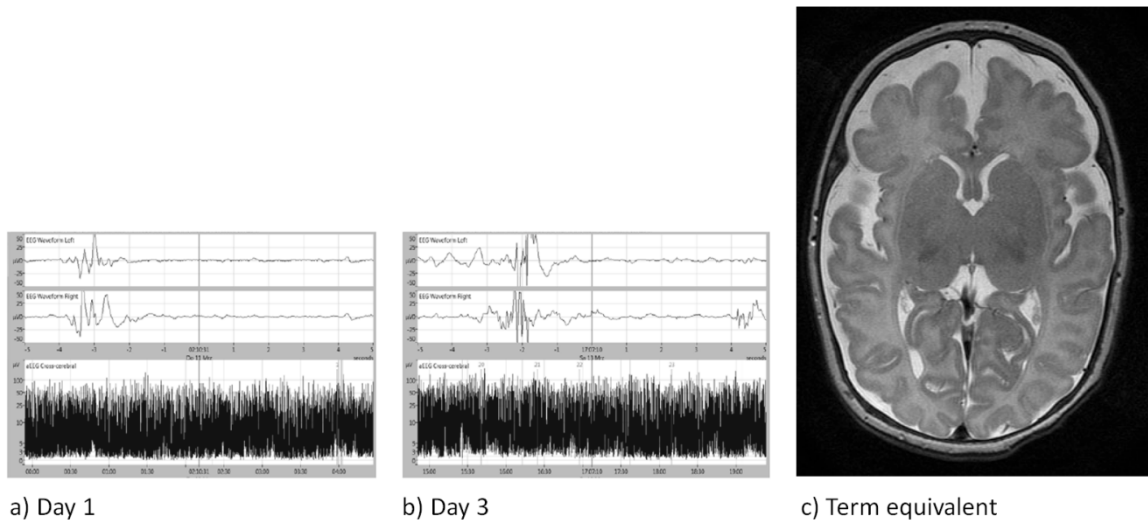
Studies on the clinical utility of aEEG in the NICU have been mainly focussed on the management of term infants affected by neonatal encephalopathy following perinatal asphyxia. In those patients, early aEEG monitoring, i.e. within 6 h after the asphyctic event, revealed to be predictive for adverse short- (127, 128) and long-term (129) outcome in cohorts of the ‘pre-cooling era’, i.e. before the introduction of therapeutic hypothermia. To date, three studies have reported predictive values of continuous aEEG monitoring in encephalopathic newborns being treated with hypothermia. They suggested that, even if aEEG in the first 24–48 hours of life may have limited predictive value in cooled patients, the persistence of aEEG background abnormality

after 48 hours and the lack of SWC recovery after 60 hours confers higher certainty of adverse outcome (66, 130, 131).

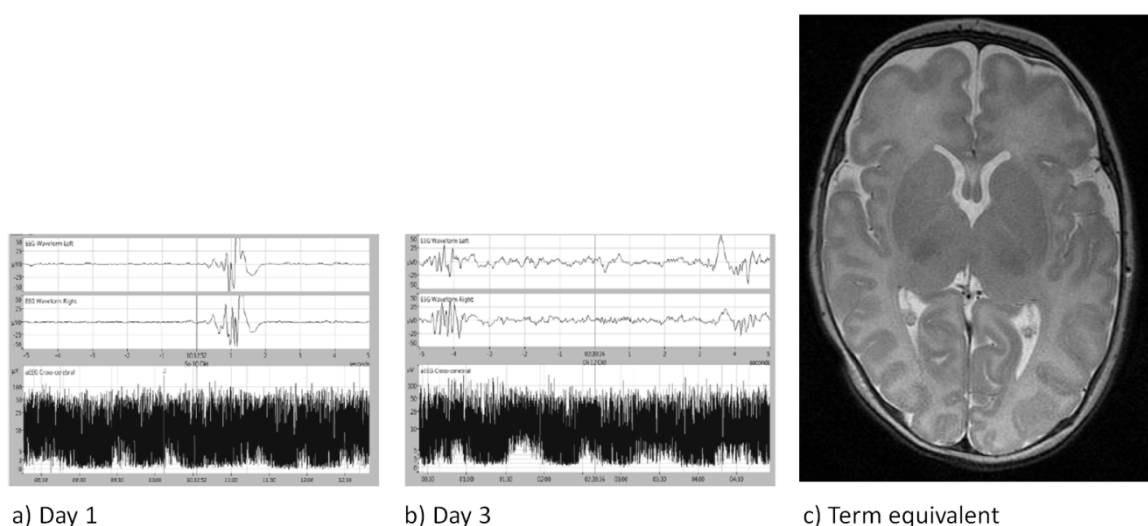
Early prediction of neurodevelopmental outcome with aEEG is more complicated in the very preterm infants than in term newborn infants, as it has been already observed with respect to the aEEG tracing interpretation. The dominant aEEG background pattern in very and extreme preterm newborn infants is discontinuous, with variable feature reflecting maturational changes in the developing brain. As a result, norm values and a classification system based on the type of background pattern have not been definitely identified for the preterm population. While the recognition of the absence of cycling activity is a relative evident task, normative references for the distinction and scoring of different grades of dysmature cycling are still limited. Further, neurodevelopmental outcome in the preterm infant is not only determined by brain lesions, which may possibly be detected by aEEG monitoring, but also by neonatal morbidities as bronchopulmonary dysplasia, retinopathy of prematurity, sepsis, as well as sex and socio-demographic factors (27, 132). In that perspective, some groups have studied the predictive value of early aEEG in preterm newborn infants with respect to the neonatal outcome (69, 70, 72, 74, 88, 112, 133-140). The assessment of the predictive value for the neurological long-term outcome of preterms by aEEG tracing however, still remains limited.

In a cohort of very preterm newborn infants we could observe that the functional brain maturity early after birth, as measured by aEEG during the first 3 days of life, significantly correlates with the structural brain maturity, as qualitatively assessed on cranial magnetic resonance imaging (cMRI) at term equivalent. Figure 9 displays two opposite examples of (figure 9.1) infant with partially absent aEEG cycling activity over the first four days of life with the correspondent cMRI sequence with features of immaturity and atrophy, and (figure 9.2) infant with relevant cycling increase on aEEG tracings over the observational time with correspondent normal cMRI sequence at term equivalent (141) (Appendix IV).

**Figure 9.1:** Development over time of the aEEG background between day 1 and 3 after birth in a preterm newborn girl of 27 5/7 weeks of gestation: a) prevalently burst suppression aEEG background pattern at day 1 after birth with total maturity score 2/13; b) progressively discontinuous aEEG background pattern with variable minimum aEEG amplitude below 5  $\mu$ V and total maturity score 2/13; and c) axial T2 weighted MR image at 38 0/7 weeks PMA; Scores: germinal matrix 3, cortical folding 2, myelination 2, bands of migration 2, total maturation score 9/21. (141)



**Figure 9.2:** Development over time of the aEEG background between day 1 and 3 after birth in preterm newborn girl of 27 4/7 weeks of gestation: a) prevalently discontinuous aEEG background pattern at day 1 after birth with total maturity score 6/13; b) progressively continuous aEEG background with more mature cycling activity and total maturity score 8/13; and c) axial T2 weighted MR image scanned at 41 0/7 weeks PMA. Scores: germinal matrix 4, cortical folding 3, myelination 2, bands of migration 4, total maturation score 14/21. (141)



### 5.6.1 Prognosis of neonatal outcome

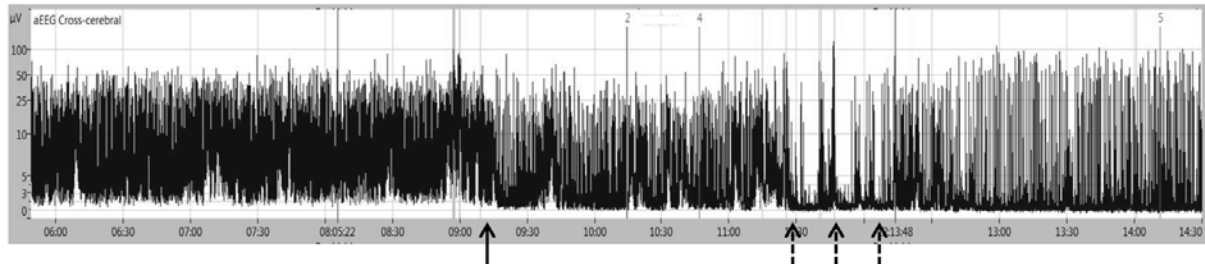
Much data from conventional EEG studies shows that the electrocortical activity is an early marker of brain damage in preterm infants during the first weeks after birth (142-144). The meaning of abnormal aEEG tracing early after birth in terms of neonatal outcome in preterm infants has been investigated by some groups since the late 1980's (133, 134). Recently, predictive values for abnormal aEEG background have been reported (69, 88, 135). However, both aEEG abnormalities and neonatal outcome are heterogeneously defined. Quantitative measurements of the degree of continuity of the aEEG background are obtained by visual analysis, percentage assessment of activity above a predefined voltage level (i.e. 3 or 5  $\mu$ V), or burst frequency assessment. Neonatal outcome is generally defined in the literature as a major neurological complication, i.e. grade III IVH or PVHI according to Volpe (145) or cystic periventricular leukomalacia (cPVL), or death.

#### *aEEG Background*

The main aEEG background abnormality characterizing the tracing of preterm infants with poor neonatal outcome compared to that of GA-matched controls, is amplitude suppression (69, 72, 112, 135-137, 139, 146). Figure 10 displays the aEEG tracing of a 2 days old preterm girl, born at 27 6/7 weeks of gestation, which is characterized by sudden amplitude suppression (continuous arrow). The discontinuous background pattern changes abruptly to a burst suppression pattern, with periods of relative long cortical suppression (dashed arrows). That episode occurred in a period when the infant was stable and corresponded to the development of a bilateral grade III IVH according to (145) diagnosed by cUS 6 hours later, with later development of posthaemorrhagic hydrocephalus.

**Figure 10:** aEEG tracing of a 2 days old preterm girl with developing bilateral grade III IVH according to (145). Sudden amplitude suppression (continuous arrow) with abrupt change from discontinuous pattern to burst suppression, with long suppression periods (dashed arrows).

27 6/7 weeks GA, day 2 after birth



The role of aEEG as additional tool for the evaluation and management of preterm infants with posthaemorrhagic hydrocephalus has been recently reported by Klebermass and associates (140), who reported in 13 of 17 patients an aEEG background deterioration before clinical signs of elevated intracranial pressure occurred, and a normalisation within a week of successful neurosurgical intervention for cerebrospinal fluid removal.

Concerning the predictive values of an abnormal aEEG background pattern observed early after birth in preterm infants, two studies (69, 137) reported amplitude suppression, defined by a decrease in the tracing continuity, as a sensitive marker for poor neonatal outcome (acute brain injury as above described or death). Please see table 3 for further details. A third recent study (135) however, provided rather high specificity and positive predictive values (PPV). This is probably the consequence of the fact that the cut-off for amplitude suppression, i.e. low amplitude voltage or burst suppression (pathologic at any GA), was quite lower than in the other studies.

**Table 3: Predictive values of amplitude suppression on early aEEG for death, P/IVH, cPVL.**

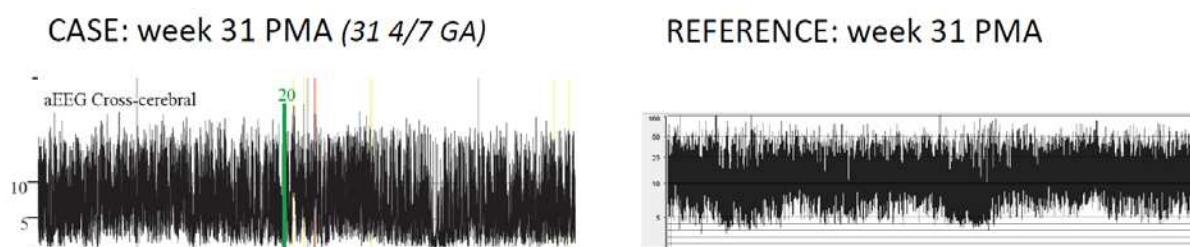
Patients (n)	aEEG within	Sensitivity	Specificity	PPV	NPV	Outcome	Ref
<29 week GA (65)	48h ab	83%	77%	45%	95%	Death / P/IVH	(137)
<32 week GA (115)	12h – 72h ab	89%	61%	-	-	P/IVH / cPVL	(69)
<29 week GA (30)	48h ab	57%	100%	100%	85%	P/IVH	(135)

GA, gestational age; h, hours; ab, after birth; PPV, positive predictive value; NPV, negative predictive value, Ref, reference; P/IVH, grade III intraventricular haemorrhage and periventricular haemorrhagic infarction according to (145); cPVL, cystic periventricular leukomalacia.

### *aEEG cycling*

Similarly, aEEG cyclicity is less commonly observed in preterm infants with poor neonatal outcome compared to GA-matched controls (69, 70, 72, 136, 137, 139). In such cases cycling activity can be completely absent during prolonged periods after birth or may be present without any sign of adequate maturation as depicted in the sequences of figure 11. Additionally, loss of aEEG cycling activity is associated with development of posthaemorrhagic hydrocephalus in preterm infants (147).

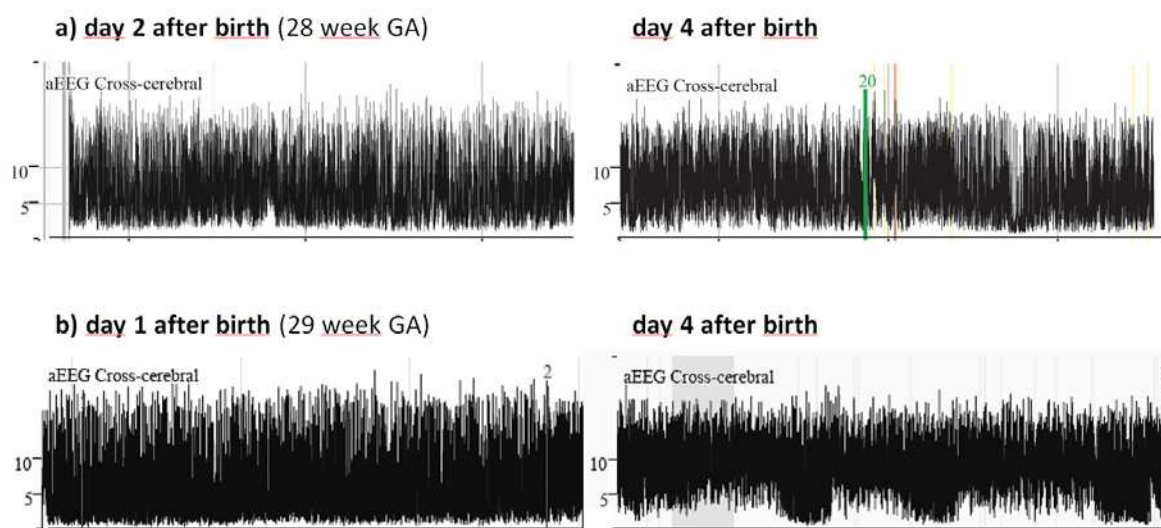
**Figure 11:** aEEG tracing of a preterm infant at the 31 week PMA with bilateral grade III IVH according to (145). No adequate maturation of the aEEG cycling activity is evident. The aEEG tracing of a neurologically healthy preterm infant at similar PMA is shown as reference.



With repeated measures analysis we investigated the trajectories over the first four days of life in very preterm newborn infants, looking at the characteristics of the developmental patterns. We observed that, while some infants showed no evident development of aEEG cycling activity as depicted in the aEEG sequences a) of figure

12, the majority of infants displayed a relevant cycling increase during the observational period as depicted in the aEEG sequences b) of figure 12. Looking for possible trajectory differences between preterm infants with severe, mild and no brain lesions as observed by cUS, we noticed that preterm infants with severe brain lesions had a significantly slower development of the aEEG cycling activity compared to those with mild or no brain lesions (72) (Appendix V). This finding remained significant after adjustment for differences in GA, birth weight, illness severity score, and sedation.

**Figure 12:** aEEG tracing at day 1 and day 4 after birth of two preterm newborn infants a) with and b) without major IVH. In case a) no evident sign of maturation of the cyclic aEEG activity is observed, while in case b) displays a relevant cycling increase during the short observational period.



The results of three studies are summarized in table 4 with respect to the predictive values of the absence of cycling activity for poor outcome (defined as mentioned above). The first two studies (69, 137) reported similar high specificity and negative predictive value (NPV), though different outcomes, and different timing of aEEG assessment between the studies. Finally, a Japanese study (70) reported a specificity and NPV of 100% of early aEEG for the prediction of cPVL in a group of 12 preterm infants.

**Table 4: Predictive values of absent cyclicity on early aEEG for death; P/IVH; cPVL.**

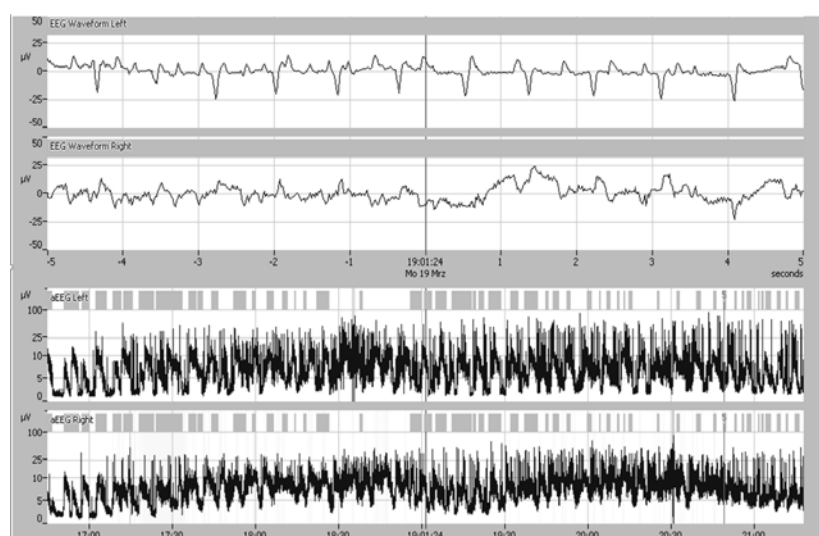
Patients (n)	aEEG within	Sensitivity	Specificity	PPV	NPV	Outcome	Ref
<29 week GA (65)	48h ab	75%	77%	43%	93%	Death / P/IVH	(137)
<32 week GA (115)	12h - 72h ab	63%	81%	-	-	P/IVH / cPVL	(69)
<32 week GA (12)	24h ab	100%	89%	75%	100%	cPVL	(70)

GA, gestational age; h, hours; ab, after birth; PPV, positive predictive value; NPV, negative predictive value, Ref, reference; P/IVH, grade III intraventricular haemorrhage and periventricular haemorrhagic infarction according to (145); cPVL, cystic periventricular leukomalacia.

### *aEEG seizures*

Seizures are known to occur more commonly in preterm infants with poor neonatal outcome compared to GA-matched controls (74, 88, 133, 136, 139), as it was the case of a late preterm infant with status epilepticus, shown in figure 13, associated to sinovenous thrombosis with large bilateral PVHI.

**Figure 13:** aEEG recording showing typical saw-tooth tracing corresponding to a status epilepticus in a late preterm newborn boy with sinovenous thrombosis. The raw EEG tracing shows epileptic activity on the left side, while suspected epileptic activity on the right side seems to be distorted by artefactual interferences.





Shah and associates reported that electrographic seizures in preterm infants observed during the first week of life by aEEG trend analysis (22% of 51 infants) are significantly associated with cerebral injury documented by cMRI exam and neonatal death (74). In table 5 the predictive values for both outcomes are shown. The low PPV of the early occurrence of electrographic seizures in preterm infants as observed by continuous aEEG monitoring is explained by the fact that in that study, among infants with seizures, a relevant proportion suffered from major neonatal complications other than cerebral injury, like necrotising enterocolitis for instance. Thus, the absence rather than the occurrence of seizures was predictive in this cohort (74).

**Table 5: Predictive values of seizures on early aEEG for death and P/IVH.**

<b>Patients (n)</b>	<b>aEEG within</b>	<b>Sensitivity</b>	<b>Specificity</b>	<b>PPV</b>	<b>NPV</b>	<b>Outcome</b>	<b>Ref</b>
<b>&lt;30 week GA (51)</b>	4d – 5d ab	45%	95%	71%	86%	Death	(74)
<b>&lt;30 week GA (51)</b>	4d – 5d ab	53%	94%	82%	80%	P/IVH	(74)

GA, gestational age; d, days; ab, after birth; PPV, positive predictive value; NPV, negative predictive value, Ref, reference; P/IVH, grade III intraventricular haemorrhage and periventricular haemorrhagic infarction according to (145).

### 5.6.2 Prognosis of outcome at early childhood

The correlation of aEEG tracing with later neurodevelopmental outcome in the preterm infants has not yet been broad investigated compared to the neonatal outcome analysis described above. Whether there is an optimal time point in assessing aEEG pattern for best prediction still remains an open question. Acute EEG stage abnormalities, characterized by acute amplitude depression, and chronic stage EEG abnormalities, characterized by disorganized patterns and delayed maturation (or dysmaturity), are associated with brain injuries and correlate with further neurodevelopment (113, 139, 148). Most of the acute changes of the EEG background are transient and gradually resolve later, being replaced by “chronic-stage” changes. Therefore, it is of interest to provide information concerning both EEG changes while monitoring brain function, which is probably best performed by prospectively repeated exams. There is some evidence that aEEG recording from the first two weeks after birth may display the best predictive values, while thereafter

predictive power is decreasing (149). As already mentioned, the analysis of aEEG tracing recorded during the first few days after birth requires particular attention because of the relative higher rate of possible confounders during that early life period, which may interfere with the tracing interpretation and may cause false negatives. Many changes in respiratory (respiratory distress, mechanical ventilation) and hemodynamic status (i.e. arterial hypotension, closure of patent ductus arteriosus) may occur, and the rate of intensive medical intervention and medication (i.e. sedation, arousing drugs) is more frequent in the first two weeks of life than thereafter (149). To date, three groups reported the predictive values of early aEEG for preterm outcome during early childhood as defined as 1.5 to 3 years of corrected age (71, 140, 150), some others reported the association between early aEEG abnormalities and further outcome in preterms (112, 146). The predictive values of decreased continuity, absent cycling activity, and seizure occurrence on early aEEG tracing for adverse outcome, defined as death or ND in preterm survivors, are reported in the following paragraphs.

#### *aEEG background*

aEEG background activity characterized by prolonged periods of amplitude suppression, defined as prolonged interburst period or decreased continuity, provides predictive outcome information within the first days of life (112, 149, 150). This has been reported for preterm infants with large IVH (88), but also irrespective of brain damage and GA at birth (71). Table 6.1 shows the predictive values of decreased continuity of aEEG background for poor outcome at early childhood in preterm infants. Despite the heterogeneity of the values, being partially explained by differences in the outcome definitions, there is a quite recognizable decrease in the false positive rate during the first weeks of life. Predictive data of EEG continuity measurements in the West and associates' study (150) were slightly lower compared with those of a neurophysiologist's interpretation, assessing interburst interval, waveforms and seizures together. In fact, visual expert examination provided lower false positives, with a sensitivity of 63%, specificity of 93%, PPV and NPV of 75% and 88% for adverse outcome at 15 months, respectively (150). Quantitative aEEG/EEG data, as the highest burst rate per hour (which correspond to the best background) provided comparable predictive information to the aEEG qualitative

assessment, without further increase in the prognostic accuracy (71) (tables 6.1 and 6.2).

**Table 6.1: Predictive values of decreased continuity for death or ND at early childhood.**

Patients (n)	aEEG within	Sensitivity	Specificity	PPV	NPV	Ref
<29 week GA (76)	1d – 2d ab	58%	72%	41%	84%	(150)
<30 week GA (49)	1d – 3d ab	89%	53%	54%	89%	(71)
< 30 weeks GA (148)	2w ab	68%	95%	95%	69%	(149)

**Table 6.2: Predictive values of increased interburst interval for death or ND at early childhood.**

Patients (n)	aEEG within	Sensitivity	Specificity	PPV	NPV	Ref
<30 week GA (49)	1d – 3d ab	89%	67%	63%	91%	(71)
<33 week GA (64)*	2d ab	70%	92%	95%	60%	(88)

ND, Neurodevelopmental disability; GA, gestational age; d, days; w, weeks; ab, after birth; PPV, positive predictive value; NPV, negative predictive value, Ref, reference; \* with grade III periventricular or periventricular haemorrhage according to Volpe (145).

### *aEEG cycling*

Hellström-Westas and associated reported that the presence of aEEG cycling activity during the first week after birth in preterm infants suffering from high grade IVH is associated with fair outcome (survived healthy or with mild cerebral palsy) at two years of corrected age (88). Concerning aEEG predictive data, the absence of cycling activity on early aEEG seems to be a quite specific marker of poor outcome in early childhood as demonstrated by table 7, which again displays the few corresponding data from the literature. In opposition to the other aEEG assessment components, absent cycling activity still provide high specific prediction of poor outcome until the fourth week of life (149). (Table 7)

### *aEEG seizures*

Among all aEEG assessment components, seizures detected on continuous cot-side electroencephalogram seem to provide the lowest predictive values. Table 8 shows

predictive values of seizures detected by aEEG for poor outcome at early childhood in preterm infants (71, 149, 150). Seizures are markers of cerebral dysfunction and are associated with the development of neonatal neurological complication (high grade IVH, cPVL, meningitis) and with abnormal outcome (74, 151). However, prediction of poor outcome by recognition of seizures by aEEG recording may be low because of two main limiting factors. On the one hand, the suboptimal level of accuracy of aEEG with respect of seizure detection (80) may explain the high false negative rate observed in two of three studies. The discrimination between abnormal neuronal activity and artefacts may be difficult and further interfere with seizure detection. On the other hand, long-term outcome of preterm infants may not only be determined by a transitory neurological dysfunction, detected in form of seizure activity in the aEEG tracing, but also by other neonatal morbidities. That may explain the higher false positive rate observed in one of three studies. It still remains to be determined whether long-term outcome in preterms may be influenced by seizure management (152). (Table 8)

**Table 7: Predictive values of absent cycling activity for death or ND at early childhood.**

Patients (n)	aEEG within	Sensitivity	Specificity	PPV	NPV	Ref
<30 week GA (49)	1d – 3d ab	58%	77%	61%	74%	(71)
<30 week GA (148)	2w ab	47%	96%	96%	50%	(149)

ND, Neurodevelopmental disability; GA, gestational age; h, hours; w, weeks; ab, after birth; PPV, positive predictive value; NPV, negative predictive value, Ref, reference.

**Table 8: Predictive values of seizures for death or ND at early childhood.**

Patients (n)	aEEG within	Sensitivity	Specificity	PPV	NPV	Ref
<29 week GA (76)	1d – 2d ab	26%	100%	100%	80%	(150)
<30 week GA (49)	1d – 3d ab	44%	43%	40%	47%	(71)
<30 week GA (148)	2w ab	11%	98%	87%	50%	(149)

ND, Neurodevelopmental disability; GA, gestational age; h, hours; w, weeks; ab, after birth; PPV, positive predictive value; NPV, negative predictive value, Ref, reference.

### *Comparison with other neurologic assessment tools*

Table 9 listed non-adjusted odds ratios for poor outcome at early childhood as defined by abnormalities observed during the first two weeks of life or at term equivalent age by four different neurological diagnostic tools from three different studies on similar preterm populations. Data relates to aEEG, as defined by a sum abnormality score, including background, cycling activity and seizure occurrence (149); severe-to-moderate abnormalities on conventional EEG (15); major brain lesions on cUS (149); and moderate-to-severe white matter abnormalities on cMRI performed at term equivalent age (12).

**Table 9: Non-adjusted odds ratios (95% confidence intervals) for poor outcome at early childhood of abnormalities on aEEG, EEG, cUS during the first two weeks of life, respectively, and cMRI at term equivalent age.**

Abnormal:	aEEG	EEG	cUS	cMRI (WM)
At:	2. week ab	2. week ab	2. week ab	40. week PMA
	(n = 143)	(n = 278)	(n = 143)	(n = 167)
<b>DQ &lt; 70</b>	16.9 (3.9-72.4)	6.9 (2.6-19)	7.8 (2.1-29.3)	3.6 / 10.3 * (1.4-8.7 / 3.5-30.8)
<b>Cerebral palsy</b>	14.7 (4.3-50.3)	12.1 (4.5-32.0)	13.4 (3.9-46.0)	9.5 (3.2-28.3)
<b>Death</b>	8.1 (1.4-45.1)	-	9.3 (1.6-51.9)	-
	Klebermass et al., 2011 (149)	Hayashi-Kurakashi et al., 2012 (15)	Klebermass et al., 2011 (149)	Woodward et al., 2006 (12)

ab, after birth; cUS, cranial ultrasound scan; PMA, postmenstrual age; cMRI (WM), cranial magnetic resonance imaging (white matter); DQ, developmental quotient, < 70 reflects an index below – 2 standard deviations from the norm 100 for mental or motor performances in (149) and (15); in (12) data about mental development and psychomotor developmental index, according to the Bayley's scales of infant development, II edition (153) are reported separately; cerebral palsy is defined according to (154) in (15) and (12).

Concerning the timing of aEEG assessment with respect to the outcome prediction, Klebermass and associates reported that the predictive value of aEEG for outcome in early childhood constantly increased, reaching its maximal values at the second week of life, while the absence of cycling activity alone remained a very specific

marker for poor outcome until the fourth week of life (149). They reported only a slight decrease of the predictive values (especially for the NPV) of cUS for poor outcome over the first four weeks of life. Hayashi-Kurakashi and associates shown that according to unadjusted analysis, EEG abnormalities in any time period within the first month of life significantly predicted poor neurodevelopmental outcome in preterm infants, while major brain lesions detected by neuroimaging techniques (cUS or cMRI) had the highest odds ratios (15). It seems however, that abnormal functional EEG findings precede structural abnormalities observed on cUS, consistent with previous reports (67, 137). cMRI in preterm infants at term equivalent age allows better quantification of differences in brain morphology than cUS (13, 14). In a recent review, Plaisier and associates investigated how cMRI in preterm infants should be timed to best predict long-term outcome. Based on literature data, they suggested that the cMRI should preferably be performed at term-equivalent age, as the individual prognostic information provided by brain magnetic resonance scanning at that period of life seems to be superior to that provided by early cMRI (155). Furthermore, cMRI exam before term equivalent age in preterm infants is more challenging for the more vulnerable, respiratory and thermoregulatory instable patient during the first few days after birth.

Data on the association between the assessment of the general movements, comparable to those of table 9, i.e. about exclusively preterm infants with similar GA, similar outcome measures and similar statistical analysis have not been published yet. This functional assessment of the neurological integrity of the NICU patient with high predictive value for the long-term neurodevelopment of full-term newborn infants (156), merits to be mentioned. The timing of this method has been defined in function of the quality of movements at three age groups according to a standard, namely preterm, writhing (i.e. term), and fidgety (i.e. third month after term) periods, the fidgety period providing the best predictive validity (156, 157). Two studies reported predictive values of the assessment of general movements for the development of cerebral palsy in preterm infants with GA below 32 (102 infants) (158) and 30 (86 infants) (159) weeks, at the corrected age of 18 and 12 months, respectively. Abnormal general movements assessed during the 36<sup>th</sup> to 44<sup>th</sup> week PMA (the writhing period) provided following predictive values: sensitivity 62-100%, specificity of 40-69%, PPV 9-29% and NPV 100-90%, while during the third month after term (the fidgety period) the results were as follows: sensitivity 50-100%, specificity 81-

86%, PPV 0.3-41%, and NPV 90-100% (158, 159). Interestingly, it has been recently reported that combining abnormal general movements at 3 months of corrected age with findings of moderate-to-severe white matter abnormalities from MRI obtained at term equivalent age significantly enhances the predictive specificity to 100% for the diagnosis of cerebral palsy in extremely preterm infants at early childhood (160).

The aim of this last paragraph is finally not to provide 1:1 data comparison between the different functional and imaging assessment tools. This is anyway not possible because only the information concerning the aEEG summary abnormality score and contemporary cUS relates to the same infant population, while data concerning conventional EEG, MRI, and general movements have been obtained from separate cohorts. More important than an academically interesting comparison between the different assessments, is the fact that this information, complementary with neonatal and psychosocial factors, could help to improve early identification of preterm infants at higher risk for adverse outcome.

## **6. Conclusion and future directions**

Very preterm infants represent a growing patient population at significant risk for cerebral injury and neurodevelopmental impairments. Based on recent and representative prospective Swiss database, this thesis demonstrates that: 1) although more than a third of extreme preterm infants still suffer from moderate or severe ND, the rate of survival without major neurologic sequelae has increased significantly over the last decade, while the mortality rate decreased in Switzerland; 2) outcome at two years of age in children surviving the neonatal period is best predicted by neonatal morbidities, among them major brain lesions; and 3) late outcome of young adults formerly born preterm with an extremely low birth weight is on overall satisfactory. The need for improved neuromonitoring, treatment, and prevention of brain lesion in the NICU is therefore high. By the current state of scientific knowledge, aEEG should become part of the daily care in every Swiss NICU as continuous neuromonitoring tool for critically ill newborn infants. This thesis demonstrates that aEEG is a valuable neurophysiologic diagnostic tool for the continuous bedside monitoring of brain function that may help clinicians in the early recognition of preterm patients at particular high risk for neurologic damage. In preterm infants compared to GA-matched controls, aEEG characteristics of severe brain lesion are amplitude suppression, absent cyclic activity, and higher likelihood of seizure activity. These findings should prompt at least an immediate cUS scan for further evaluation of brain injury. As neuroprotective studies are being conducted to improve long-term outcome in preterm infants, aEEG could play a critical role providing neurophysiological markers that would help to guide interventional strategies and to help parental counselling. In fact, the analysis of bedside aEEG early after birth may improve the identification of preterm infants at particular risk for adverse outcome, suppressed background and absent cycling activity on aEEG providing better predictive values than seizure occurrence. Some clinical conditions, the administration of certain medications, and artefactual features may, however, alter relevantly the aEEG tracing and confound its interpretation. On the other hand, preterm outcome can also be affected by non-cerebral morbidities (i.e. bronchopulmonary dysplasia) which cannot be primarily detected by aEEG monitoring. Therefore, the combination of aEEG tracing information with clinical and neuroimaging findings should be the aim of further research studies. In addition, and probably more importantly, longer follow-up protocols should be used in order to



assess the long-term prognostic relevance of early aEEG in preterm infants. The focus of further research needs to be put also on a relevant potential application of aEEG in the preterm population that may be of future clinical utility. In fact, beneath the possible role of aEEG for the early selection of patients at particular high risk of neurological complications and for possible neuroprotective intervention, continuous monitoring of the cerebral activity could support neurodevelopmental oriented care with particular attention on the premature signs of the patient's sleep-wake cycling and tracing changes in response to sensorial stimuli.

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## 9. Own contributions

### Appendix I:

Schlapbach L, Adams M, Proietti E, Aebischer M, Grunt S, Borradori-Tolsa C, Bickle-Graz M, Bucher HU, Latal B, **Natalucci G**. (2012) Outcome at two years of age in a Swiss national cohort of extremely preterm infants born between 2000 and 2008. BMC Pediatr. Epub 2012 Dec 28; 12:198. doi: 10.1186/1471-2431-12-198

### Appendix II:

**Natalucci G**, Becker J, Becher K, Bickle Graz M, Landolt M, Bucher HU (2013) Self-perceived health status and mental health outcomes in young adults born with less than 1000 g in Switzerland. Acta Paediatr. 102(3):294-9. doi: 10.1111/apa.12102

### Appendix III:

Bernet V\* and Latal B\*, **Natalucci G**, Doell C, Wohlrab G. (2010) Effect of sedation and analgesia on postoperative aEEG in newborn cardiac patients. Pediatr Res. 67(6):650-5. doi: 10.1203/PDR.0b013e3181da44ba (\*shared first authorship)

### Appendix IV:

**Natalucci G**, Ha-Vihn Leuchter R, Hüppi P, Koller B, Latal B, Bucher HU, Hagmann C. (2013) Functional brain maturation assessed during early life in preterm infants correlates with anatomical brain maturation at term equivalent age. Pediatr Res. Epub ahead of print 2013 Apr 5. doi: 10.1038/pr.2013.57

### Appendix V:

**Natalucci G**, Rousson V, Bucher HU, Bernet V, Hagmann C, Latal B. (2013) Delayed cyclic activity development on early amplitude-integrated EEG in the preterm Infant with brain lesions. Neonatology. 103(2):134-40. doi: 10.1159/000345202

## **Appendix I**

### **Outcome at two years of age in a Swiss national cohort of extremely preterm infants born between 2000 and 2008.**

BMC Pediatr. 2012; Epub 2012 Dec 28;12:198. doi: 10.1186/1471-2431-12-198

Schlapbach L, Adams M, Proietti E, Aebischer M, Grunt S, Borradori-Tolsa C, Bickle-Graz M, Bucher HU, Latal B, **Natalucci G**



## **Appendix II**

### **Self-perceived health status and mental health outcomes in young adults born with less than 1000 g in Switzerland.**

Acta Paediatr. 2013; 102(3):294-9. doi: 10.1111/apa.12102

**Natalucci G**, Becker J, Becher K, Bickle Graz M, Landolt M, Bucher HU



### **Appendix III**

#### **Effect of sedation and analgesia on postoperative aEEG in newborn cardiac patients.**

Pediatr Res. 2010; 67(6):650-5. doi: 10.1203/PDR.0b013e3181da44ba

Bernet V\* and Latal B\*, **Natalucci G**, Doell C, Wohlrab G  
(\*shared first authorship)





## **Appendix IV**

**Functional brain maturation assessed during early life in preterm infants  
correlates with anatomical brain maturation at term equivalent age.**

Pediatr Res. 2013 Apr 5. doi: 10.1038/pr.2013.57 [Epub ahead of print]

**Natalucci G**, Ha-Vihn Leuchter R, Hüppi P, Koller B, Latal B, Bucher HU, Hagmann C



## **Appendix V**

### **Delayed cyclic activity development on early amplitude-integrated EEG in the preterm Infant with brain lesions.**

Neonatology. 2013; 103(2):134-40. doi: 10.1159/000345202

**Natalucci G**, Rousson V, Bucher HU, Bernet V, Hagmann C, Latal B